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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NOAKES, SUZANNE MARIE	
ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/822,938	Applicant(s) HSIAO ET AL.	
	Examiner Suzanne M. Noakes, Ph.D.	Art Unit 1656	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 07 May 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *05 April 2007*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *54-59 and 61-78*.

   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See continuation sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Advisory Action

Status of the Application

1. Applicants filed a Notice of Appeal 05 April 2007 followed by the filing of an After Final amendment to the claims and an Affidavit filed under 37 C.F.R. 1.132 on 07 May 2007. The amendments to the claims have been entered and the affidavit considered as described below.

2. By way of After Final amendment, Applicants have added new claims 77 and 78. Thus, claims 54-59 and 61-78 are pending and the subject of this Advisory Action.

3. The Examiner would like to thank Ms. Purcell and Mr. Forman for the interview on 06 March 2007. Despite the helpful discussions on the day, it is noted, that upon review of the instant enablement rejection of record, along with the affidavit and response to the Final Office action filed by Applicants, careful reconsideration regarding the withdrawal of the instant rejection of record has resulted in the maintenance of the rejection for the reasons below.

Maintained Rejections/Objections

Claim Rejections - 35 USC § 112 – 1st paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 54-59 and 61-76 and new claims 77-88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The details of the

rejection are recited in the previous Office actions dated 20 April 2006 and 06 October 2006.

Response to Arguments and Affidavit

6. Applicant's response filed on 07 May 2007 for claims 54-59 and 61-76 have been fully considered but they are not persuasive. Furthermore, the Affidavit under 37 CFR 1.132 filed 07 May 2007 is insufficient to overcome the rejection of claims 54-59 and 61-74 based upon the 35 U.S.C. 112 1st enablement rejection as set forth in the last Office action for the following reasons.

Applicants traverse the rejection of record stating that the specification describes in Example 1 the gram staining procedure wherein a catalase assay is used to identify the Gram (+) TW-S-7-1 bacterium used in Applicants collagen extraction process. However, it is noted that this Example gives no more information that the Examiner has already argued, which is simply that whatever isolate used by Applicants simply is from the *genus* Bacillus. The method of identification is irrelevant if a skilled artisan has no idea what the starting material was so that said artisan can reproduce Applicants invention. Should the TW-S-7-1 bacterium be an actual ATTC deposit then it must therefore be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The specification does not disclose a repeatable process to obtain the microorganism and it is not apparent if the microorganism is readily available to the public. Moreover, because no taxonomic

information appears in the specification, it is not clear what the microorganism actually is. The only thing known it is a Bacillus microorganism which is a field isolate, but isolated from where or what is unclear. Again the issue of which species the field isolate from is deemed critical and the point argued in the previous Office action is reiterated here: "Which isolate/species which was used is not disclosed and as stated previously, there are approximately *193 different species* of *Bacillus* (see DSMZ document cited previously) and Applicants have not disclosed even a single species from this genus which they used in their claimed invention. Applicants recognize that different microogranisms produce different enzymes and this is stated in the specification on p. 4, 3rd sentence: "Microorganisms are capable of generating a wide array of molecules as end points to fermentation." In the instant case, the end point of fermentation and which enzymes are produced is the critical end point for Applicants invention because if the proper enzymes are not produced in the fermentation culture, then the collagen will not be broken down in the manner envisaged by the claimed invention." (see previous Office action, Response, p. 4). This point was clearly argued by Applicants in the response to the 102(b) and 103 rejections filed 13 July 2005 which was convincing enough to the Examiner so as to drop said rejections. The argument at hand regards the use Riese et al. (US 4,0646,083) who teach the "conditioning" of collagen for gelatin extraction by fermenting the collagen with proteinases extracted from *Bacillus subtilis* and *Bacillus lichenformis* Applicants stated (see p. 17 of Remarks):

> "In contrast, the Riese disclosure expressly uses enzymes to "do not attack the basic structure of collagen in order." Col. 1, lines 63-66. Ries notes later that the proteolytic enzymes avoids the "filamentous collagen molecules being split into smaller peptide fragments." Col. 2, lines 44-50."

Thus, clearly the success of Applicants instant invention requires the production of the correct enzymes produced as bi-products of fermentation, and not just any enzymes because otherwise the proteinases produced from *Bacillus subtilis* and *Bacillus lichenformis* as stated in Riese et al. would be capable of achieving the limitation of "collagen monomers".

Applicants cite *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.* to reiterate the fact that some inoperable embodiments are to be expected and just because a claim possesses inoperable embodiments that the claim is not necessarily not enabled. While this point was discussed in the interview as noted above, and the Examiner did agree that this certainly is acceptable in some terms of patentability, further consideration of the matter has led the Examiner to the following conclusion: while inoperable embodiments can be expected within an enabling disclosure and within certain claims, the instant disclosure is not deemed enabling because of the expectation of undue experimentation which will be necessary for one skilled in the art to make and use the invention as claimed. Claims 54-59 are drawn to any microorganism in existence from extremophiles to thermophiles to archae, etc. and the inordinate amount more in existence. However, as stated and noted by Applicants, the only Example which clearly sets forth what kind of microorganism, is Example 1 wherein the field isolate used in the invention has been identified as one from the genus of *Bacillus* which as noted above has 193 different species. However, *Bacillus* is not representative of all microorganisms, which include gram (-) microorganisms which Applicants have not tested or used whatsoever in the instant disclosure. Furthermore, there are many more

which include aerobes, obligate aerobes, anaerobes, obligate anaerobes or facultative anaerobes.

Applicants have further noted that the Examiner's concerns about how mostly collagen monomers were formed was unclear. To allay these concerns, Applicants have in response re-ordered the steps of independent claims 54 and 68 to recite that the collagen monomers appears at the end of the claims rather than the middle and that now the collagen production of monomers need not be predominant (e.g. mostly collagen monomers) but rather 10% of the total collagen production weight. The new limitation now recites "wherein the precipitated collagen product comprises collagen monomers weighing at least 10% of the weight of the total collagen in said collagen product." However, this does not remedy or answer any questions regarding what or how produces the collagen monomers. Clearly it is some enzyme produced in the fermentation process, however, which enzyme is wholly unclear. Applicants arguments on p. 14, actually support that different organisms will produce different and varying amounts of $\alpha\beta\gamma$ forms of collagen monomers. "In addition yeast fermentation (Example 5) versus bacterial fermentation (Examples 2-4 and 6) may result in different proportions of the β and γ forms of collagen. Regardless, Applicants' Examples 2-6 all result in the isolation of collagen monomers in the amount required by the pending claims". In another statement regarding the amount of β and γ forms of collagen, it is stated: "Applicants submit that *these differences* are to be expected and *are based on differences in*, for example, *starting material and microorganism employed for fermentation.*" (see p. 13, last line to beginning of p. 14). Thus, the conclusion drawn

from these statements is quite clear, different microorganisms will produce varying amounts of the different forms of collagen. While Applicants state that all of them produce the amount required, e.g. 10% by weight of mostly collagen monomers, this statement alone is enough to, at the very least, cast considerable doubt on the success of any or all microorganisms which are limitations for claims 54-59 and 61-67, if not the entire genus of Bacillus (claims 68-78). In addition, new claims 77 and 78 require production percentages of 50 and 80%, respectively.

In addition, Applicants have attempted to clarify the Examples in the specification for Examples 2-6. Applicants have provided a "new Figure 3" wherein it appears that Applicants re-performed the Experiment and ran a new SDS-gel at 8% rather than 10% and also loaded less sample volume. While this is helpful in some sense, the Example still demonstrates that production of significant quantities of the gamma forms and beta forms. Furthermore, the adjustment of 10% to 8% SDS-gel should only affect the migration of the bands and nothing else. As far as "overloading" the previous gel, it does not seem that the gels were overloaded as clear separation of the two alpha bands was achieved.

The Examiner recognizes that the art might not be complex but this does not preclude the requirement for experimentation as undue because the test of enablement is not whether any experimentation is necessary, but whether, if experimentation that is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

7. Regarding the Affidavit filed under 37 CFR 1.132 by Dr. Nam, this disclosure also in unconvincing. The Affidavit is re-stated by Applicants in the Remarks section and all issues have been addressed above. It is noted that Figure 3 was re-done in order to adjust the gel % in order to achieve better separation and to also not "over load" the wells which also obtains better separation. While the Examiner acknowledges these facts, it is still readily apparent that there is considerable amounts of β and γ forms, while only 10% of the total weight need be monomers (e.g. the alpha form), it is wholly unclear how the limitations of new claims 77 and 78 are met for these examples (e.g. 50% and 80% of the total weight is collagen monomers).

8. As a final note regarding the unpredictability of the production and success of using any microorganism, or those which are generally regarded as safe (GRAS) or any from the genus *Bacillus*, Schallmey et al. (Can. J. Micro. 2004, 50(1):1-17) make clear that each species of *Bacillus* (let alone any or all microorganism or GRAS microorganisms) produce vastly different bi-products. While much is known about the genus *Bacillus*, it is also known selecting the appropriate species of *Bacillus* is essential depending upon the application or outcome which one desires. For instance, Table 1 gives several enzymes produced by different Bacillus species, Table 2 lists the major enzyme produced and the industrial applicability of each: for example, *B. calusii, B. amloliquefaciens, B. halodurans* which produce alkaline proteases for detergents; while alkaline amylase for detergents is produced by *B. lichenformis, B. halmapalus*; α-Amylase for starch is produced by *B. lichenformis*; Pullulanase for starch is produced by *B. stearathermophilus*; Glucose isomerase for starch by *B. acidipullulyticus*, *B.*

deramificans; Amylase (for textiles) by *B. halodurans*; Pectate lyases, alkaline amylase and mannanase for textiles is made by most *Bacillus* species; etc. These are just some examples to illustrate that all *Bacillus* species do not produce the same enzymes and thus it would be unpredictable to know which essential enzymes are required in the fermentation process which seems to be essential in Applicants invention. Applicants, however, have not provided any sort of details about what species of *Bacillus* is used which gives rise to the appropriate enzymes which breaks down the collagen in the appropriate manner. There is not even a hint or clue as to which 'category' of *Bacillus* species would be applicable and successful to the present invention. Schallmey et al. further illustrate that not every enzyme is produced by *Bacillus* by stating for example: "Numerous species of *Bacillus* have been explored for alkaline protease production, but most potential alkaline proteases producers are strains of *B. amyloliquefaciens*, *B. lichenformis, B. majovensis, and B. subtilis.*" (see p. 4, 2nd column, last paragraph). This statement suggests that only certain species will produce certain by-products and enzymes.

Thus, as noted above, it would be unpredictable for one skilled in the art which Bacillus species to use, which ones would be successful, let alone the claims which are drawn to all microgransims and GRAS microorganisms. This would thus lead to the conclusion that considerable undue experimentation would be required by one skilled in the art.

5/21/07

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